```
=> d que stat l17
L11        1860 SEA FILE=HCAPLUS ABB=ON  ?DEMINERAL?(W)?BONE?(W)?MATRIX? OR
                DBM
L12          83 SEA FILE=HCAPLUS ABB=ON  L11 AND (?BONE?(W)?MORPHOGENET?(W)?PRO
                TEIN? OR ?COLLAGEN?(L)?PROTEIN?)
L13           7 SEA FILE=HCAPLUS ABB=ON  L12 AND ?CROSSLINK?
L16           4 SEA FILE=HCAPLUS ABB=ON  L13 AND ?COMPOSITION?
L17           7 SEA FILE=HCAPLUS ABB=ON  L13 OR L16

=> d ibib abs l17 1-7
```

NO

L17 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:1004968 HCAPLUS
DOCUMENT NUMBER: 140:8881
TITLE: Allograft bone **composition** having a gelatin binder
INVENTOR(S): Merboth, Barbara L.; Sunwoo, Moon Hae; Gertzman, Arthur A.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 983,526.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002192263	A1	20021219	US 2002-150097	20020520
US 6030635	A	20000229	US 1998-31750	19980227
US 6437018	B1	20020820	US 2000-515656	20000229
US 2003206937	A1	20031106	US 2001-983526	20011024
WO 2003099236	A1	20031204	WO 2003-US14534	20030519

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 1998-31750	A2	19980227
US 1999-365880	B2	19990803
US 2000-515656	A2	20000229
US 2001-983526	A2	20011024
US 2002-150097	A	20020520

AB The invention is directed toward an osteoimplant for application to a bone defect site to promote new bone growth at the site which comprises a new bone growth inducing **composition** of demineralized allograft bone material mixed with an aqueous phosphate buffered gelatin which when lyophilized to remove water from the **composition crosslinks** the gelatin to form a solid structure. For example, a **crosslinked** gelatin bone formulation of 50% gelatin mixture, 40% **demineralized bone matrix (DBM)**, and 10% of sodium hyaluronate paste was prepared 7.35. The formulation was wet with phosphate

buffered saline (PBS) pH = 7.35. The **composition** was flexible, strong, and slightly brittle. After freeze drying, the tissue was rehydrated with 10 mL PBS and at 60 min, it was slightly flexible with bone loosened around the ends.

L17 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:202522 HCAPLUS
DOCUMENT NUMBER: 138:226801
TITLE: A **crosslinked** collagen biomaterial
INVENTOR(S): Duneas, Nicolaas; Lutz, Martina Magdel
PATENT ASSIGNEE(S): Bone SA, S. Afr.
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020327	A2	20030313	WO 2002-IB3576	20020904
WO 2003020327	A3	20040610		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

ZA 2002007160	A	20030405	ZA 2002-7160	20020905
PRIORITY APPLN. INFO.:			ZA 2001-7385 A	20010906

AB A method of producing a **crosslinked collagen** biomaterial includes the step of providing a **collagenous** biomaterial and irradiating the **collagenous** biomaterial with γ-irradiation at a dose of 20-160 kGy. The **collagen** biomaterial is provided in the form of a gel and is produced by extracting bone powder or tendon. A **composition** comprising a **crosslinked collagen** gel 1000, together with **bone morphogenetic proteins** 0.5-2.5 and **demineralized bone matrix** 500 mg induced new bone formation when injected into soft tissues of the rodent and bony sites of the human.

L17 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:112616 HCAPLUS
DOCUMENT NUMBER: 132:330982
TITLE: Proteolysis of human bone collagen by cathepsin K: characterization of the cleavage sites generating the cross-linked N-telopeptide neoepitope
AUTHOR(S): Atley, L. M.; Mort, J. S.; Lalumiere, M.; Eyre, D. R.
CORPORATE SOURCE: Orthopaedic Research Laboratories, University of Washington, Seattle, WA, USA
SOURCE: Bone (New York) (2000), 26(3), 241-247
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An immunoassay for cross-linked N-telopeptides of type I **collagen** (NTx) in urine or serum has proven to give a sensitive index of osteoclast-mediated bone resorption. We show that recombinant human cathepsin K is highly active in releasing the NTx neoepitope in 100% yield from bone type I **collagen.** Cathepsins S, L, and B were also active but at 57%, 36%, and 27% of the yield of K, resp. The matrix **metalloproteinases** that were tested, stromelysin, **collagenase** 3, or matrilysin, did not produce any immunoreactivity. Cathepsin K also acted on **demineralized bone matrix**, releasing NTx epitope and completely dissolving the bone particles in 24-48 h. Proteolytic cleavage of a G-L peptide bond in the α2(I)N-telopeptide was shown to be required for recognition by monoclonal antibody 1H11. Peptide anal. identified bonds in the N-telopeptide and helical **crosslinking** domains adjacent to the **crosslinking** residues at which cathepsin K cleaved in bone **collagen.** The sites were consistent with the known substrate specificity of cathepsin K, which prefers a hydrophobic residue or proline in the critical P2 position. The NTx peptides generated by cathepsin K were of low mol. weight, in the range previously found in human urine. Because cathepsin K appears to be essential for the normal resorption of mineralized bone matrix by osteoclasts, these findings help explain the specificity and responsiveness of NTx as a marker of osteoclastic bone resorption in vivo.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:624020 HCAPLUS
DOCUMENT NUMBER: 129:250241
TITLE: Bone paste comprising a bioabsorbable osteogenic compound in a gelatin matrix
INVENTOR(S): Wironen, John F.; Grooms, Jamie M.
PATENT ASSIGNEE(S): University of Florida Tissue Bank, Inc., USA; University of Florida Research Foundation, Inc.
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9840113	A1	19980917	WO 1998-US4904		19980312
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
US 2002098222	A1	20020725	US 1997-816079		19970313
AU 9865528	A1	19980929	AU 1998-65528		19980312
EP 984797	A1	20000315	EP 1998-911607		19980312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2001514565	T2	20010911	JP 1998-539819		19980312
PRIORITY APPLN. INFO.:			US 1997-816079	A	19970313
			WO 1998-US4904	W	19980312

AB A bone paste useful in the orthopedic arts, for example in the repair of

non-union fractures, periodontal ridge augmentation, craniofacial surgery, implant fixation, impaction grafting, or any other procedure in which generation of new bone is deemed necessary, is provided by a **compn** . comprising a substantially bioabsorbable osteogenic compound in a gelatin matrix. In various embodiments, the osteogenic compound is selected from (1) **demineralized bone matrix** (**DBM**); (2) bioactive glass ceramic, Bioglass, bioactive ceramic, calcium phosphate ceramic, hydroxyapatite, hydroxyapatite carbonate, corraline hydroxyapatite, calcined bone, tricalcium phosphate, or like material; (3) **bone morphogenetic protein**, TGF-β, PDGF, or mixts. thereof, natural or recombinant; and (4) mixts. of (1)-(3). The bone paste contains dry demineralized bone 0-40, lyophilized thermally **crosslinkable** gelatin 20-45, Bioglass 0-40%, and bone morphogenic protein 0.001 mg/mL. The bone paste was osteoinductive when implanted in rats.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:455578 HCAPLUS
DOCUMENT NUMBER: 125:151095
TITLE: Comparative histological study of mineralizations after intramuscular implantations of heat-denatured **demineralized bone matrix** gelatin, heat-denatured demineralized tooth, and cross-linked collagen
AUTHOR(S): Ninomiya, Masami
CORPORATE SOURCE: Sch. Dent., Univ. Tokushima, Tokushima, 770, Japan
SOURCE: Shikoku Shigakkai Zasshi (1996), 9(1), 77-97
CODEN: SSZAED; ISSN: 0914-6091
PUBLISHER: Shikoku Shigakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB I.m. implantation of **demineralized bone matrix** gelatin (BMG) is known to form spherical mineralized deposits in the implant prior to bone tissue formation induced by **bone morphogenetic protein** (BMP). This type of mineralization is called "acellular mineral deposition (AMD)", which is not associated with osteogenic cells. In the present study, heat-denatured BMG, heat-denatured demineralized tooth, and calf skin type I **collagen** cross-linked with glutaraldehyde were resp. implanted into the rectus abdominis muscles in rats. Then mineralized deposits formed in the implants after the resp. implantations were compared by means of histol. anal.by using light and electron microscopes. Compns. of these deposits were also analyzed by electron probe x-ray microanal. Heat-denatured BMG, which was prepared at 150° for 30 min to inactivate non-**collagenous proteins** including BMP (NCP), was used to investigate whether NCP had some roles in AMD process. Heat-denatured demineralized tooth and **crosslinked collagen** were also used to examine the relations of AMD with calcification of dentin and with matrix **collagen.** In heat-denatured BMG, spherical mineralized deposits initially appeared at day 3 and then gradually increased in the size and the number Finally these deposits fused with each other to occupy the whole implant at day 14. Similar observations were obtained in the case of heat-denatured demineralized tooth implant. Mineralization was progressed in one way from enamel side to dental pulp side. Predentin area did not easily mineralized during the exptl. period. In **crosslinked collagen**, fiber-like mineralized deposits were scattered along **collagen** fiber bundles at day 3. These deposits gradually

increased in the number and invaded into the surrounding **collagen** fibers to increase in the size, and then these deposits fused with each other to occupy the whole implant at day 14. Bone and cartilaginous tissues did not appear around the implants, and also there were no osteoblast- and osteoclast-like cells in any implants. Mineralized deposits were formed compactly showing needle-shaped crystals in all implants. **Composition** anal. revealed that these deposits showed a similar mol. ratio of calcium to phosphorus. AMD occurs with no relation to the subsequent bone tissue formation and that NCP never have any roles in AMD process. AMD physicochem. occurs depending on cross-linked **collagen** of matrix and that AMD observed in the implanted dentin may take place in the physiol. mineralization because of the morphol. similarity between AMD and globular dentin.

L17 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:621918 HCAPLUS
DOCUMENT NUMBER: 121:221918
TITLE: Effects of lathyritic drugs and lathyritic **demineralized bone matrix** on induced and sustained osteogenesis
AUTHOR(S): Di Cesare, Paul E.; Nimni, Marcel E.; Yazdi, Mohamadreza; Cheung, David T.
CORPORATE SOURCE: Cartilage Bone Res. Cent., Hosp. Joint Dis. Orthopaedic Inst., New York, NY, USA
SOURCE: Journal of Orthopaedic Research (1994), 12(3), 395-402
CODEN: JOREDR; ISSN: 0736-0266
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Demineralized bone matrix** was implanted in normal and lathyritic rats. At 2 wk, the bone that formed in the lathyritic animals had an elevated alkaline phosphatase activity and a reduced calcium content compared with the controls. Four weeks after implantation, these biochem. parameters were reversed, with a decrease in alkaline phosphatase activity and an increase in calcium content to control levels. The histol. of the recovered implants revealed new bone formation. Lathyritic **demineralized bone matrix** was prepared from bones of rats fed β-aminopropionitrile for 2 wk (2-wk BAPN-**DBM**) or 4 wk (4-wk BAPN-**DBM**), and was implanted in normal rats. Two weeks after implantation, both prepns. of lathyritic **demineralized bone matrix** demonstrated early bone formation, although alkaline phosphatase activity and calcium content were reduced. By 4 wk after implantation, no biochem. or histol. evidence of bone formation remained at the site of the 4-wk BAPN-**DBM** implants; continued but reduced bone formation was observed at the site of the 2-wk BAPN-**DBM** implants. Reconstitution of inactivated normal **demineralized bone matrix** with the guanidine-soluble exts. restored the osteoinductive capacity. However, reconstitution of inactivated lathyritic **demineralized bone matrix** (4-wk BAPN-**DBM**) failed to restore the osteoinductive capacity. These results indicate that the degree of **crosslinking** of the **collagen** matrix that acts as a carrier for osteoinductive **proteins** plays a key role in inducing and sustaining osteogenesis.

L17 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:436094 HCAPLUS
DOCUMENT NUMBER: 109:36094
TITLE: Biochemical differences between dystrophic calcification of cross-linked collagen implants and mineralization during bone induction

AUTHOR(S): Nimni, Marcel E.; Bernick, Sol; Cheung, David T.; Ertl, Delia C.; Nishimoto, Satoru K.; Paule, Wendelin J.; Salka, Carl; Strates, Basil S.
CORPORATE SOURCE: Sch. Med., Univ. Southern California, Los Angeles, CA, 90007, USA
SOURCE: Calcified Tissue International (1988), 42(5), 313-20
CODEN: CTINDZ; ISSN: 0171-967X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ectopic calcification of diseased tissues or around prosthetic implants can lead to serious disability. Therefore, calcification of implants of glutaraldehyde-**crosslinked collagenous** tissues and reconstituted **collagen** was compared with mineralization induced by **demineralized bone matrix** (**DBM**). Whereas implants of **DBM** accumulated large amts. of Ca and a bone-specific γ-carboxyglutamic acid **protein** (BGP or osteocalcin) following implantation in both young and older rats, implants of **crosslinked** pericardial tissue calcified with only traces of BGP. Glutaraldehyde-**crosslinked DBM** failed to calcify after implantation in 8-mo-old rats for 2-16 wk. Implants of **crosslinked** type I **collagen** exhibited small calcified deposits 2 wk postimplantation but Ca content eventually dropped to levels equal to those of soft tissues as the implants were resorbed. The Ca content of **DBM** implanted in 1- and 8-mo-old rats reached comparable levels after 4 wk, but the BGP content was approx. twice as high in the younger animals than in the older ones. Glutaraldehyde-**crosslinked** implants of **DBM**, tendon, and cartilage calcified in young but not in old animals. This form of dystrophic calcification was associated with only trace amts. of BGP. Alkaline phosphatase activity was high in implants of **DBM** and undetectable in implants of **crosslinked collagenous** tissues. These results show that implants of glutaraldehyde-**crosslinked collagenous** tissues and reconstituted **collagen** calcify to different extents depending upon their origin and the age of the host, and that the mechanism of dystrophic calcification differs from the process of mineralization associated with bone induction as reflected by alkaline phosphatase activity and BGP accumulation.

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=> d que stat l19
L11        1860 SEA FILE=HCAPLUS ABB=ON  ?DEMINERAL?(W)?BONE?(W)?MATRIX? OR
                DBM
L12          83 SEA FILE=HCAPLUS ABB=ON  L11 AND (?BONE?(W)?MORPHOGENET?(W)?PRO
                TEIN? OR ?COLLAGEN?(L)?PROTEIN?)
L13           7 SEA FILE=HCAPLUS ABB=ON  L12 AND ?CROSSLINK?
L14          10 SEA L13
L15           8 DUP REMOV L14 (2 DUPLICATES REMOVED)
L18           1 SEA L15 AND ?COMPOSIT?
L19           8 SEA L15 OR L18

=> d ibib abs l19 1-8

L19  ANSWER 1 OF 8     MEDLINE on STN
ACCESSION NUMBER:   94267648     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 8207593
TITLE:              Effects of lathyritic drugs and lathyritic
                    demineralized bone matrix on
                    induced and sustained osteogenesis.
AUTHOR:             Di Cesare P E; Nimni M E; Yazdi M; Cheung D T
CORPORATE SOURCE:   Cartilage and Bone Research Center, Hospital for Joint
                    Diseases Orthopaedic Institute, New York, New York 10003.
CONTRACT NUMBER:    AG02577 (NIA)
     AM37042-01 (NIADDK)
SOURCE:             Journal of orthopaedic research : official publication of
                    the Orthopaedic Research Society, (1994 May) 12 (3)
                    395-402.
                    Journal code: 8404726. ISSN: 0736-0266.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals; Space Life Sciences
ENTRY MONTH:        199407
ENTRY DATE:         Entered STN: 19940721
                    Last Updated on STN: 19940721
                    Entered Medline: 19940711
```

AB **Demineralized bone matrix** was implanted in normal and lathyritic rats. At 2 weeks, the bone that formed in the lathyritic animals had an elevated alkaline phosphatase activity and a reduced calcium content compared with the controls. Four weeks after implantation, these biochemical parameters were reversed, with a decrease in alkaline phosphatase activity and an increase in calcium content to control levels. The histology of the recovered implants revealed new bone formation. Lathyritic **demineralized bone matrix** was prepared from bones of rats fed beta-aminopropionitrile for 2 weeks (2-week BAPN-**DBM**) or 4 weeks (4-week BAPN-**DBM**), and was implanted in normal rats. Two weeks after implantation, both preparations of lathyritic **demineralized bone matrix** demonstrated early bone formation, although alkaline phosphatase activity and calcium content were reduced. By 4 weeks after implantation, no biochemical or histological evidence of bone formation remained at the site of the 4-week BAPN-**DBM** implants; continued but reduced bone formation was observed at the site of the 2-week BAPN-**DBM** implants. Reconstitution of inactivated normal **demineralized bone matrix** with the guanidine-soluble extracts restored the osteoinductive capacity. However, reconstitution of inactivated lathyritic **demineralized bone matrix** (4-week BAPN-**DBM**) failed to restore the osteoinductive capacity. These results indicate that the degree of **crosslinking** of the **collagen** matrix that

acts as a carrier for osteoinductive **proteins** plays a key role in inducing and sustaining osteogenesis.

L19 ANSWER 2 OF 8 MEDLINE on STN
ACCESSION NUMBER: 90125632 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2612151
TITLE: Dystrophic calcification and mineralization during bone induction: biochemical differences.
AUTHOR: Nimni M E; Bernick S; Ertl D C; Nishimoto S K; Paule W J; Villanueva J
CORPORATE SOURCE: Department of Biochemistry, University of Southern California School of Medicine, Los Angeles.
SOURCE: Connective tissue research, (1989) 20 (1-4) 193-204. Journal code: 0365263. ISSN: 0300-8207. Report No.: NASA-90125632.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900307

AB The calcification of implants of glutaraldehyde-cross linked **collagenous** tissues and **collagen** was studied in young and old rats and compared to bone induction by non-**crosslinked** osteogenically active **demineralized bone matrix** (**DBM**). Glutaraldehyde-**crosslinked** implants of **DBM**, tendon, and cartilage calcified in young but not in old animals and accumulated only trace amounts of BGP (Bone Gla **protein**, osteocalcin). Alkaline phosphatase activity and BGP was high in implants of **DBM** and undetectable in **crosslinked** implants. To try and understand why bone formation is so significantly reduced in older Fischer 344 rats, we developed a system which consists of cylinders of **DBM** sealed at the ends with a Millipore filter. Cells originating from 20 day old embryo donors were introduced into the chambers prior to subcutaneousmplantation. After 4 weeks of implantation in 26 month old rats, the cylinders containing embryonic calvaria or muscle cells were found to be full of bone and/or cartilage.

L19 ANSWER 3 OF 8 MEDLINE on STN
ACCESSION NUMBER: 90010456 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2794638
TITLE: Dystrophic calcification and mineralization during bone induction: biochemical differences.
AUTHOR: Nimni M E
CORPORATE SOURCE: Department of Biochemistry, University of Southern California School of Medicine, Los Angeles.
SOURCE: Nippon Seikeigeka Gakkai zasshi, (1989 May) 63 (5) 630-42. Journal code: 0413716. ISSN: 0021-5325. Report No.: NASA-90010456.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 198910
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19891031

AB The calcification of implants of glutaraldehyde-**crosslinked**

collagenous tissues and **collagen** was studied in young and old rats and compared to bone induction by non-**crosslinked** osteogenically active **demineralized bone matrix** (**DBM**). Glutaraldehyde-**crosslinked** implants of **DBM**, tendon, and cartilage calcified in young but not in old animals and accumulated only trace amounts of BGP (Bone Gla **protein**, osteocalcin). Alkaline phosphatase activity was high in implants of **DBM** and undetectable in **crosslinked** implants. To try and understand why bone formation is so significantly reduced in older Fischer-344 rats, we developed a system which consists of cylinders of **DBM** sealed at the ends with a Millipore filter. Cells originating from 20-day-old embryo donors were introduced into the chambers prior to subcutaneous implantation. After 4 weeks of implantation in 26-month-old rats, the cylinders containing embryonic calvaria or muscle calls were found to be full of bone and/or cartilage.

L19 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 1988:313408 BIOSIS
DOCUMENT NUMBER: PREV198886030446; BA86:30446
TITLE: BIOCHEMICAL DIFFERENCES BETWEEN DYSTROPHIC CALCIFICATION OF CROSS-LINKED COLLAGEN IMPLANTS AND MINERALIZATION DURING BONE INDUCTION.
AUTHOR(S): NIMNI M E [Reprint author]; BERNICK S; CHEUNG D T; ERTL D C; NISHIMOTO S K; PAULE W J; SALKA C; STRATES B S
CORPORATE SOURCE: 2400 S FLOWER ST, LOS ANGELES, CALIF 90007-2697, USA
SOURCE: Calcified Tissue International, (1988) Vol. 42, No. 5, pp. 313-320.
CODEN: CTINDZ. ISSN: 0171-967X.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 3 Jul 1988
Last Updated on STN: 3 Jul 1988

AB Ectopic calcification of diseased tissues or around prosthetic implants can lead to serious disability. Therefore, calcification of implants of glutaraldehyde-cross-linked **collagenous** tissues and reconstituted **collagen** was compared with mineralization induced by **demineralized bone matrix** (**DBM**). Whereas implants of **DBM** accumulated larger amounts of calcium and a bone-specific-γ-carboxyglutamic acid **protein** (BGP or osteocalcin) following implantation in both young and older rats, implants of cross-linked pericardium calcified with only traces of BGP. Glutaraldehdye-cross-linked **DBM** failed to calcify after implantation in 8-month-old rats for 2-16 weeks. Implants of **crosslinked** type I **collagen** exhibited small calcific deposits 2 weeks postimplantation but calcium content eventually dropped to levels equal to those of soft tissues as the implants were resorbed. The calcium content of **DBM** implanted in 1- and 8-month-old rats reached comparable levels after 4 weeks, but the BGP content was approximately twice as high in the younger animals than in the older ones. Glutaraldehyde-cross-linked implants of **DBM**, tendon, and cartilage calcified significantly in young but not in old animals. This form of dystrophic calcification was associated with only trace amounts of BGP. Alkaline phosphatase activity was high in implants of **DBM** and undetectable in implants of cross-linked **collagenous** tissues. These results show that implants of glutaraldehyde-cross-linked **collagenous** tissues and reconstituted **collagen** calcify to different extents depending upon their origin and the age of the host, and that the mechanism of dystrophic calcification differs significantly from the process of mineralization associated with bone inductions as

reflected by alkaline phosphatase activity and BGP accumulation.

L19 ANSWER 5 OF 8 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 1999261735 EMBASE
TITLE: Osteogenesis imperfecta: Bone turnover, bone density, and ultrasound parameters.
AUTHOR: Cepollaro C.; Gonnelli S.; Pondrelli C.; Montagnani A.; Martini S.; Bruni D.; Gennari C.
CORPORATE SOURCE: C. Cepollaro, Institute of Internal Medicine, University of Siena, Viale Bracci 2, Siena, Italy
SOURCE: Calcified Tissue International, (1999) 65/2 (129-132). Refs: 24
ISSN: 0171-967X CODEN: CTINDZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We studied 21 patients (11 men and 10 women) with osteogenesis imperfecta (OI) and 21 age- and sex-matched controls. In all patients we measured serum levels of total alkaline phosphatase (ALP), type I procollagen carboxy-terminal propeptide (PICP), osteocalcin (BGP), urinary excretion of hydroxyproline (HOP/Cr), and pyridinoline **crosslinks** (Pyr/Cr). Bone mineral density was measured at the distal radius (BMD-R) and at the lumbar spine (BMD-LS) by dual X-ray absorptiometry (DXA). Ultrasound parameters were also performed at the calcaneous with the Achilles device and at the phalanxes with **DBM** Sonic 1200. A significant reduction ($P < 0.001$) in BMD and in ultrasound parameters was found in OI patients compared with normals. PICP was significantly reduced in the OI patients compared with controls ($P < 0.001$); other markers of bone turnover were higher in OI than in controls, but the difference did not reach the statistical significance. A significant correlation ($P < 0.05$) was found between PICP and BMD at the lumbar spine and between PICP and ultrasound parameters at the calcaneous. On the basis of our data, we conclude that patients with OI show low values of BMD and ultrasound parameters; therefore in these patients, not only is bone mass disturbed but also bone quality. The reduced levels of PICP in OI patients confirm that most OI patients have defects in collagen I biosynthesis. These defects may contribute to the fragility of OI bone by interfering with complete mineralization and/or normal tissue structure. PICP may be considered a useful marker in the clinical management of OI.

L19 ANSWER 6 OF 8 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-682664 [73] WPIDS
DOC. NO. NON-CPI: N2002-539008
DOC. NO. CPI: C2002-192528
TITLE: Injectable bone like implant used for repairing bone defect and injury comprises bone like compound and hydrophobic carrier or degradable component.
DERWENT CLASS: A96 B04 D22 P34
INVENTOR(S): WIRONEN, J F
PATENT ASSIGNEE(S): (WIRO-I) WIRONEN J F; (REGE-N) REGENERATION TECHNOLOGIES INC
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002058755	A2	20020801	(200273)*	EN	15

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ
LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD
SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
US 2002193883 A1 20021219 (200303)
EP 1359951 A2 20031112 (200377) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
AU 2002251861 A1 20020806 (200427)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002058755	A2	WO 2002-US3092	20020125
US 2002193883	A1 Provisional	US 2001-263972P	20010125
		US 2002-56217	20020125
EP 1359951	A2	EP 2002-720893	20020125
		WO 2002-US3092	20020125
AU 2002251861	A1	AU 2002-251861	20020125

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1359951	A2 Based on	WO 2002058755
AU 2002251861	A1 Based on	WO 2002058755

PRIORITY APPLN. INFO: US 2001-263972P 20010125; US 2002-56217 20020125

AN 2002-682664 [73] WPIDS

AB WO 200258755 A UPAB: 20021113

NOVELTY - A bone-like implant comprises at least one bone-like compound and a hydrophobic carrier or at least one degradable component.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for production of the implant which comprises mixing at least one bone-like compound in a hydrophobic carrier or a degradable component and concurrently or subsequently combining with an aqueous phase to form a combined mixture.

ACTIVITY - Osteopathic.

MECHANISM OF ACTION - None given in the source material.

USE - Used for repairing a bone defect and injury.

ADVANTAGE - The implant is capable of aqueous sintering or curing and increasing its porosity in situ.

Dwg.0/0

L19 ANSWER 7 OF 8 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN.

ACCESSION NUMBER: 1999-326321 [27] WPIDS
CROSS REFERENCE: 1989-178217 [24]
DOC. NO. NON-CPI: N1999-244804
DOC. NO. CPI: C1999-096403
TITLE: Production of biocompatible delivery systems for repair of osseous defects.
DERWENT CLASS: A96 B04 B07 C03 C07 P32
INVENTOR(S): JEFFERIES, S R
PATENT ASSIGNEE(S): (BIOC-N) BIOCOLL LAB INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5904718	A	19990518	(199927)*		12

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5904718	A	Cont of	US 1986-844886	19860327
		CIP of	US 1987-80145	19870630
		Cont of	US 1987-119916	19871113
		Cont of	US 1991-718914	19910624
		Cont of	US 1992-892646	19920602
		Cont of	US 1993-57951	19930129
		Div ex	US 1995-422745	19950414
		CIP of	US 1995-470368	19950606
			US 1997-872210	19970609

PRIORITY APPLN. INFO: US 1997-872210 19970609; US
1986-844886 19860327; US
1987-80145 19870630; US
1987-119916 19871113; US
1991-718914 19910624; US
1992-892646 19920602; US
1993-57951 19930129; US
1995-422745 19950414; US
1995-470368 19950606

AN 1999-326321 [27] WPIDS
CR 1989-178217 [24]
AB US 5904718 A UPAB: 19990714
NOVELTY - Method uses **collagen** and demineralized bone particles. It may contain a maximum of 20 % inorganic materials. The product is densified by compression, and additional osteogenic factors, mitogens, drugs or antibiotics may be incorporated in it. Inorganic materials may be bound to the organic matrix via pre-coating with a calcium or hydroxyapatite binding **protein**, peptide or amino acid. The materials display long lasting drug release characteristics.

DETAILED DESCRIPTION - Methods of making biocompatible delivery system comprise (a) dispersing bioactive **protein**, peptide or drug with **protein** particles chosen from **demineralized bone matrix** optionally extracted in chaotropic agents and/or reconstituted collage; (b) dispersing the particles in an aqueous solution of 0.002-0.25 weight % **crosslinking** agent and surface activating or partially **crosslinking** the particles; (c) removing the particles from the aqueous dispersion; and (d) adding organic matrix to the particles. An INDEPENDENT CLAIM is also included for a similar method of making biocompatible delivery system in which the bioactive **protein**, peptide or drug is dispersed within coated inorganic particles with a **protein**-based surface layer bound to them.

USE - Used to manufacture biocompatible delivery systems (claimed). Used to manufacture **protein**-based structures that delivery drugs or other agents including antibiotics, **bone morphogenetic protein**, insulin-like growth factor, nerve growth factor and human, bovine or porcine growth hormones in a controlled and stable manner. Used to prepare bone repair materials.

ADVANTAGE - Method improves binding and reactivity of **protein** -based or -coated particles to organic matrixes. Materials display lasting drug-release characteristics. Bone repair materials have improved

cohesive and physical strength for use in stress-bearing defects or where the ability to produce and maintain the specific shape of an implant is important. Inorganic particles in the materials are not easily displaced or dislodged from the matrix. Materials induce bone when implanted into animals or humans and have stress-bearing properties early after implantation.
Dwg.0/0

L19 ANSWER 8 OF 8 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-506489 [43] WPIDS
DOC. NO. NON-CPI: N1998-394814
DOC. NO. CPI: C1998-152868
TITLE: Implantable bone paste for inducing new bone growth - comprises gelatin matrix and bio-absorbable osteogenic compound, especially **demineralised bone matrix.**
DERWENT CLASS: B04 D22 L02 P34
INVENTOR(S): GROOMS, J M; WIRONEN, J F
PATENT ASSIGNEE(S): (UYFL) UNIV FLORIDA RES FOUND INC; (UYFL-N) UNIV FLORIDA TISSUE BANK INC; (GROO-I) GROOMS J M; (WIRO-I) WIRONEN J F
COUNTRY COUNT: 73
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9840113	A1	19980917	(199843)*	EN	39
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AU BA BB BG BR CA CN CU CZ EE GE GW HU ID IL IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA US UZ VN YU					
AU 9865528	A	19980929	(199906)		
EP 984797	A1	20000315	(200018)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
CZ 9903236	A3	20000816	(200048)		
SK 9901257	A3	20000814	(200051)		
HU 2000001811	A2	20001030	(200064)		
JP 2001514565	W	20010911	(200167)		38
AU 2002022995	A	20020502	(200236)#		
US 2002098222	A1	20020725	(200254)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9840113	A1		WO 1998-US4904	19980312
AU 9865528	A		AU 1998-65528	19980312
EP 984797	A1		EP 1998-911607	19980312
			WO 1998-US4904	19980312
CZ 9903236	A3		WO 1998-US4904	19980312
			CZ 1999-3236	19980312
SK 9901257	A3		WO 1998-US4904	19980312
			SK 1999-1257	19980312
HU 2000001811	A2		WO 1998-US4904	19980312
			HU 2000-1811	19980312
JP 2001514565	W		JP 1998-539819	19980312
			WO 1998-US4904	19980312
AU 2002022995	A	Div ex	AU 1998-65528	19980312
			AU 2002-22995	20020307
US 2002098222	A1		US 1997-816079	19970313

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9865528	A Based on	WO 9840113
EP 984797	A1 Based on	WO 9840113
CZ 9903236	A3 Based on	WO 9840113
HU 2000001811	A2 Based on	WO 9840113
JP 2001514565	W Based on	WO 9840113

PRIORITY APPLN. INFO: US 1997-816079 19970313; AU 2002-22995 20020307

AN 1998-506489 [43] WPIDS

AB WO 9840113 A UPAB: 19981028

An implantable bone paste **composition** comprises gelatin as a carrier for substantially bioabsorbable osteogenic components for use in a patient in need of new bone growth.

The gelatin is thermally **crosslinkable** at or slightly above the temperature of the organism into which it is to be implanted, preferably about 38 deg. C, and is in amount 20-45 weight%.

The osteogenic component is selected from:

(i) **demineralised bone matrix** (**DBM**);

(ii) bioactive glass ceramic, BIOGLASS (RTM), bioactive ceramic, calcium phosphate ceramic, hydroxyapatite, hydroxyapatite carbonate, corraline hydroxyapatite, calcined bone, tricalcium phosphate or mixtures;

(iii) **bone morphogenetic protein**, TGF-beta, PDGF or mixtures, natural or recombinant; and

(iv) mixtures of (i) - (iii).

The gelatin, the **demineralised bone matrix** or both are derived from the species into which the bone paste is to be implanted.

The **DBM** is in amount 0-40 (preferably 15-33) weight%.

The bioactive glass is BIOGLASS (RTM), especially of diameter 0.5-710 mm.

Component (ii) is in amount 0-40 wt.%.

The **composition** comprises antibiotics, bone morphogenetic or other **proteins**, whether derived from natural or recombinant sources, wetting agents, glycerol, carboxymethyl cellulose (CMC), growth factors, steroids, non-steroidal anti-inflammatory compounds or combinations, and comprises 0.0001-0.1 mg/ml **bone morphogenetic protein.**

The **composition** is freeze dried.

The gelatin is human, bovine, ovine, equine, canine or mixtures, preferably derived from human **collagen** sources (especially human skin, bone, cartilage, tendon, connective tissue or mixtures) via enzymatic, acid or alkaline extraction. The gelatin has a molecular weight greater than 50,000 daltons.

Preferably, the osteogenic component is powdered **DBM**, in amount 0-40 wt.%, with particles of size 80-850 mm diameter, provided that if the **DBM** is absent, then a bone growth factor (especially morphogenetic **protein**, TGF-b or mixtures) is present at a concentration of at least 0.0001 mg/ml.

The **composition** further comprises cortical, cancellous or cortical and cancellous bone chips, of size 80 mm to 10 mm.

USE - For inducing bone formation in vivo, e.g. repair of non-union fractures, periodontal ridge augmentation, arthrodesis of spinal or other joints, spinal fusion procedures and implant fixation (all claimed); also in craniofacial surgery and impaction grafting.

ADVANTAGE - The bone paste is easy to handle and store, adheres to the implantation site, is both osteo-conductive and osteoinductive, is thermally **crosslinkable** and bioabsorbable.
Dwg.0/4